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The Influence of Chronic Stress on Dementia-Related Diagnostic Change in Older Adults

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Abstract

Increased susceptibility of the aging brain to both chronic stress and incipient dementia-related neuropathology may accelerate cognitive decline. We investigated associations between chronic stress and diagnostic change in 62 individuals (mean age=78.7) participating in an Alzheimer's disease research center longitudinal study. Subjects, diagnosed at baseline as cognitively normal (CN) or Mild Cognitive Impairment (MCI) were followed an average of 2.5 years. Senior neurologists, blind to detailed measures of stress and cognition, assigned diagnoses annually. Logistic regression analyses assessed accuracy with which measures of stress (event-based ratings, cortisol levels) predicted conversion to MCI and dementia. Eleven individuals with MCI at baseline received a dementia diagnosis during follow-up. Sixteen converted from CN to MCI. Prolonged, highly stressful experiences were associated with conversion from MCI to dementia. The cortisol awakening response, with age and education, was associated with diagnostic change to MCI. Cortisol measures were not associated with progression from MCI to dementia, and there was no association between stressful experiences and change to MCI. Mechanisms associated with

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the transition from normal cognition to MCI may differ from those associated with diagnostic change to dementia. These findings could facilitate identification of interventional strategies to reduce risk of decline at different stages of susceptibility.

Keywords

chronic stress; aging; Alzheimer's disease; mild cognitive impairment; dementia; diurnal rhythm; cortisol awakening response

INTRODUCTION

The negative effects of stress on health have been acknowledged in the scientific literature for decades. More recently, however, investigators have focused on the effects of stress, particularly chronic stress, on the brain. Life event checklists [1, 2] and levels of the stress hormone cortisol [3-7] are among the most commonly used measures of chronic stress. Cognitive decline and associated diagnoses are often targeted as proxies for stress-related neuropathologic changes. Stress-related cognitive decline is thought to result from the effects of prolonged elevations of cortisol, a hypothalamic-pituitary-adrenocortical (HPA) axis response to chronic stress. This response targets specific brain regions including the hippocampus, amygdala, and prefrontal cortex (PFC) [8]. The hippocampus, the region that has received the most attention as a target of HPA axis response [5, 6, 9], is critical for certain types of memory [10-12] and is considered the initial site of the neuropathology of Alzheimer's disease (AD) [13], the most common form of dementia. The relationship between chronic stress and cognitive decline is particularly important for the health of older adults who are more susceptible to HPA axis dysfunction [12, 14-16] and at greater risk for developing dementia [16, 17]. Cognitive decline could result from additive effects in which chronic stress increases vulnerability to other types of neuropathologic insults [18] or vice versa. On the other hand, recent animal studies have shown a more direct or possibly causative link between stress and neuropathology associated with dementia, demonstrating that stress is associated with synapse loss [19], increases in amyloid β-peptide [20-22], and tau accumulation and phosphorylation [21, 22].

Regardless of the mechanism, the effects of chronic stress on cognition may depend on the extent of existing neuropathologic changes. Very early cognitive changes in older adults are often relatively circumscribed and cause minimal interference with daily functioning. This level of cognitive decline usually is identified as Mild Cognitive Impairment (MCI) [23] and is sometimes considered a "preclinical" stage of dementia. In a recent longitudinal study [24], we found that highly stressful events were associated with memory decline in MCI subjects over a 2- to 3-year period. However, a high level of cortisol (determined by the mean of five measures distributed throughout the day) was not associated with decline in subjects with MCI. These data suggest a differential effect of cortisol level on cognition depending on extent of neuropathologic change, a finding supported by results from a another study measuring both cognitive performance and neuropathologic changes in rats [25].

Numerous studies have identified associations between measures of chronic stress and cognitive decline. Identifying methods to better characterize chronic stress in aging, however, may have a significant impact on the relevance of these associations. Previous studies have measured primarily event-based stress using simple checklists that do not consider context and, therefore, may overlook important details such as threat severity and duration and multiple instances of events. In the current study, we used a comprehensive measure of stressful events and difficulties (Life Events and Difficulties Schedule; LEDS) [26]

that considers contextual details, documents multiple occurrences, and uses strategies to improve response reliability.

Previous studies focusing on cortisol levels as a measure of stress have targeted different aspects of the cortisol diurnal cycle [27-29]. For example, an overall diurnal average, as well as single measures at specific times of the day have been used. Another aspect frequently cited is the morning Cortisol Awakening Response (CAR), an index of HPA activity [27, 30] that in healthy individuals is defined as a sharp rise in cortisol release from the level at morning awakening to the "peak" approximately 30 minutes later. Investigators reported a consistent increase of at least 50% within the first 30 minutes after awakening in over 500 healthy subjects ranging in age from 18 to 71 years [31], confirming and extending findings concerning a normal cortisol diurnal rhythm from previous studies [30, 32, 33]. Of particular importance for this study are numerous reports of a decline in the CAR percent change in response to prolonged stress [27, 30, 34-36]. There is evidence that the size of the CAR is independent of the cortisol diurnal mean that takes a range of daytime samples into account [37], and that significant neuropathology (i.e., hippocampal) is associated with the absence of a rise in cortisol in response to awakening [34, 38] and to psychosocial stress [39]. While the exact function of the CAR is unknown, some investigators note that it may represent an HPA axis response activated endogenously by the act of awakening [30, 40]. Other investigators have characterized the sharp increase of the CAR as a reflection of the recall and anticipation of upcoming demands of the day (i.e., prospective memory) [27, 41]. We used a measure of the CAR as one feature of the diurnal cycle, but addressed the utility of two additional aspects, 1) average of the five diurnal samples (awakening, 30 minutes post awakening, 2PM, 4PM, bedtime) (diurnal mean) and 2) average of the afternoon and evening (2PM, 4PM, bedtime) samples (post-peak mean) to assess their associations with progression of cognitive decline over individualized follow-up intervals. Finally, accepting the assumption that diagnostic status represents neuropathologic changes, we used diagnostic status to stage progression. Our goal was to investigate the effects of behavioral measures and biomarkers of chronic stress as they relate to diagnostic change from MCI to dementia and from CN to MCI over a mean follow-up interval of 2.5 years. That is, we examined whether the effects of specific longitudinal measures of chronic stress improve prediction of change in diagnosis at two discrete levels of disease severity.

METHODS

Participants

Volunteers over the age of 65 and living independently were recruited from the UCSD Shiley-Marcos Alzheimer's Disease Research Center and Memory Screening Clinic. Sixty-two participants with at least three visits over follow-up were included. Individuals were excluded if found to have dementia, a significant medical disorder (e.g., insulin-dependent diabetes, chronic inflammation), or a prominent psychiatric condition (e.g., depression [42]; Post Traumatic Stress Disorder [43]), or if using corticosteroid medications that could affect daily cortisol levels. Topical corticosteroids were permitted, as were steroidal inhalants if discontinued the day before and the day of sampling. Non-steroidal anti-inflammatory (NSAID) (19 percent of subjects), hormonal (14 percent), narcotic (10 percent), anxiolytic (17 percent), and thyroid (29 percent) medications were allowed if the participant was on a stable dose for at least 6 months prior to baseline. We used statistical analyses to determine whether any of these medications had a significant effect on cortisol level.

Each participant was functioning independently in daily activities according to a knowledgeable informant, the majority of whom were spouses. Neuropsychological testing included measures of global cognition (Dementia Rating Scale; DRS [44]), memory (e.g., California Verbal Learning Test [45]), attention (e.g. Digit Span [46]), executive functions (e.g.,

Trail Making [47], Wisconsin Card Sort Test [48]), visuospatial ability (e.g., Block Design [49]), and language (e.g., Boston Naming Test [50], Verbal Fluency [51]). There were 29 CN and 33 MCI subjects at baseline. MCI subjects were classified as amnestic, single domain (n=21), non-amnestic, single domain (n=9: 8 executive function, 1 visuospatial), and multiple-domain that included memory impairment (n=3). No participant met criteria for dementia using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition or NINCDS-ADRDA criteria [52]. Subjects attended an average of 4.9 visits (SD=1.9); mean follow-up was 2.5 years (SD=1.1).

General Procedure

After reading the study description, the subject and informant signed separate written informed consents approved by the UCSD Human Research Protections Program. The informant usually joined the participant for the LEDS interview, but if unable, consented to provide information by phone. Measures of stress were obtained at baseline and thereafter at 6-month intervals; neurological, neuropsychological, and medical evaluations were completed annually.

Diagnostic Procedure

Diagnoses were made by senior neurologists based on functional, neurological, medical, and limited neuropsychological (yes/no to questions of memory deficits and ≥2 areas of impairment) information. A diagnosis of MCI-single domain was based on Petersen criteria requiring impairment in one area of cognitive functioning and essentially intact functional capacity [23]. A diagnosis of MCI-multiple domains was assigned if the subject had mild impairment in more than one cognitive domain, but did not have sufficiently severe cognitive or functional impairment to meet criteria for dementia. All study personnel were blind to stress measures and details of the neuropsychological battery.

Assessment of Chronic Stress

The Life Events and Difficulties Schedule (LEDS) [26] is a semistructured interview in which the participant reviewed a list of events and difficulties divided into categories (e.g., health, finances) to identify potentially stressful experiences during the 12 months prior to baseline and 6 months prior to each follow-up visit. The LEDS is based on the premise that experiences that cause considerable long-term threat are likely to be associated with medical and psychiatric disorders. It emphasizes the chronicity of ongoing difficulties (>2-week duration), as well as discrete events serious enough to cause long-term threat. Following methods previously described [53], the interviewer probes for information about event context (e.g., duration) and constructs a detailed description used by a trained professional to determine degree of threat (high versus low) for each event and difficulty. Only those experiences determined to be severely threatening events or marked difficulties over the "long-term" receive a high stress rating.

Cortisol measures—Sampling cortisol in saliva is a reliable, non-invasive method to assess circulating cortisol levels [54, 55] and HPA axis function. Cortisol has been shown to be highly stable under a broad range of handling and temperature storage conditions [56-58].

For each visit, participants followed detailed instructions in their homes to produce five saliva samples within one day using "Salivettes" (Sarstedt Inc., Newton, NC, USA). Samples were produced at awakening, 30 minutes later, 2 pm, 4 pm, and bedtime and refrigerated until delivered in person to study personnel. Samples then were frozen (-20°C) until delivered to the General Clinical Research Center Core Laboratory for analysis. In this study and prior studies from the Core Laboratory, no sample degradation has been observed due to study design, methodology, or sample handling. Measures of cortisol response over

time included the average of all five diurnal samples (diurnal mean), the average of the 2 PM, 4 PM, and bedtime samples (post-peak mean), and the CAR. The CAR was calculated by dividing the difference between the awakening and 30-minute post awakening samples by the awakening measure.

Cortisol EIA kits (Cat# 1-3002) were purchased from Salimetrics LLC, State College, PA. Samples, standards, controls and Cortisol-HRP conjugate were added to a micro-plate coated with mAb to cortisol and incubated at room temperature for 1 hour; unbound components were washed and bound cortisol-HRP was measured using tetramethylbenzidine (TMB) substrate. The color was read on a Spectramax M-5 (Molecular Devices, Sunnyvale, CA) multifunctional plate reader equipped with SoftmaxPro v5.4 (SMP 5.4), and a 5-parameter sigmoid minus curve fit determined unknown concentrations. The intra and inter assay precisions were 0.01-2.5 percent and 3.0-8.0 percent respectively. The CV of duplicates varied from 0.01 to 2.5 percent.

Statistical analyses

We investigated two types of diagnostic change: 1) from a baseline diagnosis of MCI to a diagnosis of dementia, and 2) from a baseline diagnosis of CN to a diagnosis of MCI. P-values were considered significant if less than 0.05. Three subjects with a baseline diagnosis of MCI and a subsequent persisting diagnosis of CN were considered CN throughout.

In order to assess whether there was an effect of medications on cortisol level, we used t-tests to compare cortisol mean values for all subjects divided by whether they were on or off each medication (i.e., NSAID, hormonal, narcotic, anxiolytic, thyroid). These comparisons yielded no significant differences. In addition, t-tests yielded no significant differences in the means or variances of the CAR when all subjects were divided by gender or by median split on time of awakening or age [27]. Stress measures were longitudinal and included the total number of high stress LEDS ratings and the cortisol diurnal mean, post-peak mean, and the CAR averaged for each subject over individualized length of follow-up. Six variables including the total number of high stress ratings, one measure of cortisol, variables considered risk factors for dementia [age, education, presence or absence of at least one Apolipoprotein-E e4 allele (APOE-e4)] and gender were included in each of the logistic regression analyses. All variables entered were continuous except gender and APOE-e4 status.

Since predictive accuracy is based on the fitted model in the logistic regression and is likely to overestimate the ability of the model to predict diagnostic change, we used 10-fold cross-validation to adjust for “out of sample” differences and to estimate sensitivity and specificity of the fitted model.

RESULTS

Eleven of the 33 participants with a diagnosis of MCI at baseline (33.3%) received a diagnosis of dementia during the follow-up interval; twenty-two retained a diagnosis of MCI. Four of the 11 who changed received a dementia diagnosis after 1 year, two after 2 years, four after 3 years, and one after 4 years. Sixteen of the 29 subjects who were CN at baseline received a diagnosis of MCI during the follow-up interval. The remaining 13 CN subjects remained cognitively intact. Ten of the 16 who changed received an MCI diagnosis after 1 year, four after 2 years, and two after 3 years. There were three CN subjects who progressed to MCI and subsequently to dementia. These subjects were included only in the analyses addressing the change from CN to MCI, and only their visits prior to conversion to dementia were considered.

Table 1 shows means and standard deviations for baseline age, education, baseline DRS score, and longitudinal stress measures for all subjects Also shown are percentages of subjects who were female, diagnosed MCI at baseline, and possessed at least one APOE-e4 allele. Table 2 shows the same measures for subjects divided by type of diagnostic change (i.e., CN to MCI and MCI to dementia).

Logistic Regression Analyses

Each logistic regression model to predict diagnostic change included 6 variables: age, education, gender, APOE-e4 allele status, and longitudinal stress measures (i.e., total number of LEDS high ratings, one of 3 cortisol measures). The overall chi-square values for all three models predicting diagnostic change from MCI to dementia were significant (see Table 3), as was one predictor variable, the total number of high stress LEDS ratings. Based on 10-fold cross-validation, sensitivity was 53.8 percent and specificity, 91.6 percent.

The same six predictor variables were entered to assess the ability to classify individuals progressing from a diagnosis of CN to MCI. The overall chi-square values for all three models were significant (see Table 4). Age and education were retained in the regression equation in all three models regardless of the cortisol measure included. However, only one measure of cortisol, the CAR, was retained along with age and education. For this model, sensitivity was 79.9 and specificity, 69.7, based on 10-fold cross-validation.

DISCUSSION

Previous studies have provided evidence of a link between chronic stress and dementia-related diagnostic change in older adults [59, 60]. We addressed this association using a comprehensive, longitudinal assessment of chronic stress based on life events and difficulties (LEDS) and three cortisol measures derived from samples extending across the diurnal cycle. We found that diagnostic change to dementia was associated with a relatively greater number of highly stressful life events and difficulties, but not with cortisol measures. Change from CN to MCI, however, was associated with a relatively lower level of one cortisol measure, the CAR, but not with other cortisol measures or the number of stressful life experiences.

The results addressing diagnostic change from MCI to dementia are consistent with those from a previous study [24] in which memory decline in MCI subjects was associated with stressful life experiences. This suggests that prolonged stress is affecting aspects of the HPA axis other than or in addition to changes in overall cortisol release. The cortisol response may impact brain regions to a lesser degree as neuropathologic compromise progresses to later stages of MCI and ultimately to dementia. It is possible that once the hippocampus reaches a certain level of compromise such as that identified in MCI [61], there is a shift in the regulatory mechanism from the hippocampus to other regions involved in HPA axis regulation (e.g., prefrontal cortex), leading to deficits in additional cognitive domains (e.g., problem solving) [62] and dementia.

While the current study did not show a relationship between the cortisol diurnal mean and conversion to MCI or dementia, we did find that a widely studied aspect of the cortisol diurnal cycle, the CAR [8, 27, 30-38, 40, 41], was useful in predicting diagnostic change in early (CN to MCI) stages of cognitive decline. This cortisol response to stress may signal damage to neurons and their connections in early stages of neuropathologic changes, a finding consistent with the notion that mechanisms associated with the transition to MCI may differ from those associated with the transition to dementia. Additional evidence for this differential effect is supplied by a study [25] showing that prolonged glucocorticoid treatment in rats pre-screened for cognitive impairment had a negative effect on subsequent learning

and memory in the “non-impaired” group, but not in the “impaired” group. The authors noted a greater percent increase in cell damage in the hippocampus (CA1 region) in “non-impaired” subjects relative to those “impaired.” Findings from a recent study addressing memory performance in healthy, human subjects [63] also suggest that the association between cortisol and memory in aging depends on the presence or absence of cognitive impairment assumed to reflect neuropathologic changes; in the MCI group, high cortisol levels were associated with poorer learning and immediate memory, and in healthy elderly, high cortisol levels were associated with better performance on delayed memory. While these findings seem inconsistent with those of other studies drawing the same conclusion, it is difficult to compare the results due to significant methodological differences. Unlike our study, the Souza-Talarico et al. study [63] included slightly younger, less educated subjects, measured memory performance at one time point, assessed visual memory (i.e., 10 line drawings) only, and obtained one saliva sample for the cortisol measure at a variable time point within two hours of awakening. Additional longitudinal studies are necessary to understand how cortisol dynamics affect cognition as older individuals progress through stages of increasing impairment.

A normal CAR has been defined as a sharp increase in cortisol release from morning awakening to the “peak” approximately 30 minutes later [31]. Findings from the current study suggest that the CAR is involved in, or reflects mechanisms involved in, the transition from intact cognitive functioning to MCI. There is evidence that the size of the CAR is independent of the average of cortisol measures from samples taken across the day, and changes in the CAR have been associated with HPA axis dysregulation, hippocampal damage, and even developmental/personality factors (e.g., self-esteem) [8]. One interpretation of its function [27] is that the CAR increases in anticipation of daily activities at awakening; the sharp increase in cortisol may decrease when impaired prospective recall precludes this anticipatory response. Other investigators [64] have proposed a process that releases the sensitivity of the adrenal response (e.g., cortisol) to pituitary activity from a pre-awakening reduction, then increases the sensitivity post-awakening in response to light. The latter is mediated by an extra-pituitary pathway to the adrenal via the suprachiasmatic nucleus, a central pacemaker for circadian rhythms. While these ideas do not provide an obvious explanation for the association between the CAR and the transition to MCI, they provide directions for additional studies to address relationships among cortisol circadian rhythm, HPA axis regulation, involvement of specific brain regions, and cognitive decline in aging.

In order to apply the study findings to clinical practice, they must be replicated in larger, independent subject samples. Cautious speculation, however, could lead to clinically useful ideas. Since models addressing progression to dementia showed good specificity but relatively lower sensitivity, we might predict that individuals with existing cognitive impairment (i.e., MCI) but relatively low chronic stress based on events and difficulties are not likely to progress rapidly to dementia. We, however, would expect less accurate predictions for those experiencing significant chronic stress. For the model addressing progression from CN to MCI, both sensitivity and specificity were only moderately elevated when the CAR was entered as a continuous variable. However, of the eight subjects with a CN diagnosis at baseline and a change in the CAR greater than 50% over follow-up, only two (25%) progressed to MCI; of the 21 subjects with a CN diagnosis at baseline and a change in the CAR less than 50% over follow-up, 14 (67%) progressed to MCI. The CAR cut point of 50 percent change reported in a large sample by Wust et al. [31] could prove useful if presented with other information (e.g., age, education) in a clinical setting.

One limitation of the study is the relatively small sample size that may have precluded detection of effects that would have been identified with a larger sample size. A second limitation, given our specific aims and methodology, is the absence of information

concerning the effects of additional factors that could influence how stress affects diagnostic change (e.g., coping strategies, lifetime stressors). Third, the percentage of subjects who progressed from CN to MCI was higher than expected. The volunteer status of subjects may have introduced selection bias by attracting subjects with concerns about memory. A significant proportion of the CN subjects had memory complaints at enrollment; it is possible that some of the complaints were associated with deficits not detected on neuropsychological testing [65, 66]. Finally, survival analysis would have been a likely statistical candidate for addressing diagnostic change over time. Subjects received diagnoses annually, and we know only that diagnostic change occurred at some point in the 12 months between visits; therefore, these data are interval censored. Since standard survival analysis (e.g., Cox Proportional Hazards regression) was developed for dealing with right-censored data (i.e., exact survival time becomes incomplete at the end or right side of follow-up), we concluded that fitting such a model would produce biased and potentially misleading results.

Despite limitations, findings from this study suggest an important link between specific measures of stress and diagnostic change that, with appropriate replication in larger, randomized samples, could improve our ability to estimate level of risk for cognitive decline in older adults. Disruption of this link using low-cost, low-risk behavioral interventions designed to modify responses to stress could greatly enhance efforts to prevent or slow disease progression in individuals at heightened risk for dementia.

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Table 1

Means and standard deviations (SD) for variables describing total sample (n=62) at baseline and over individualized follow-up.

	Mean	SD
Age (years) (baseline)	78.7	5.5
Education (years)	15.0	3.0
Mattis DRS total (baseline)	136.1	5.0
Longitudinal Measures		
High LEDS ratings	3.3	3.1
Diurnal cortisol (nmol/L)	5.7	1.8
CAR (% change)	21.1	51.5
Post-peak cortisol (nmol/L)	3.3	1.3
Follow-up interval (years)	2.5	1.1
Percentage of Subjects		
MCI versus CN (baseline)	53.2	
Female	56.5	
≥ 1 APOE-e4	45.2	

DRS = Mattis Dementia Rating Scale
LEDS = Life Events and Difficulties Schedule
Diurnal cortisol=mean of samples (awakening, 30 minutes later, 2 PM, 4 PM, bedtime)
CAR = Cortisol Awakening Response; percent change from awakening to 30 minutes later
Post-peak cortisol = mean of the 2 PM, 4 PM, and bedtime measures
APOE-e4 = Apolipoprotein-E e4 allele

Table 2

Means and standard deviations (SD) for variables describing sample divided by type of diagnostic conversion: CN to MCI (n=16) or MCI to dementia (n=11) over individualized follow-up.

	CN to MCI		MCI to Dementia	
	Mean	**SD**	**Mean**	**SD**
Age (years) (at baseline)	79.9	6.1	80.8	5.0
Education (years)	14.3	3.5	15.8	1.7
Mattis DRS total (at baseline)	139.2	3.0	132.4*	5.7
Longitudinal Measures				
Total high LEDS ratings	3.1	3.2	4.7	2.1
Diurnal cortisol (nmol/L)	5.6	2.3	5.8	1.4
CAR (% change)	10.4	46.5	17.2	56.8
Post-peak cortisol (nmol/L)	3.4	1.9	3.2	1.1
Follow-up interval (years)	2.4	0.93	2.5	1.1
Percentage of Subjects				
MCI versus CN (at baseline)	0.0		100.0	
Female	75.0		54.5	
≥1 APOE-e4 allele	31.2		36.4	

t-tests:

* $p<.05$

CN = Cognitively Normal
MCI = Mild Cognitive Impairment
DRS = Mattis Dementia Rating Scale
LEDS = Life Events and Difficulties Schedule
Diurnal cortisol = mean of samples (awakening, 30 minutes later, 2 PM, 4 PM, bedtime)
CAR = Cortisol Awakening Response; percent change from awakening to 30 minutes later
Post-peak cortisol = mean of the 2 PM, 4 PM, and bedtime measures
APOE-e4 = Apolipoprotein-E e4 allele

Table 3

Variables retained in the logistic regression analyses with conversion from **MCI to dementia** over individualized follow-up as the dependent variable and age at baseline (years), education (years), gender, presence or absence of APOE-e4 allele, total high LEDS ratings over follow-up, and a designated cortisol measure over follow-up as predictor variables.

Variables	OR	95% CI for OR		Effect Size [a]	Wald	p-value
Model 1 [b]						
Chi-square = 8.47 p<.01						
Total High LEDS Ratings	1.67	1.11	2.52	2.47	6.08	0.01
Model 2 [c]						
Chi-square = 8.47 p<.01						
Total High LEDS Ratings	1.67	1.11	2.52	2.47	6.08	0.01
Model 3 [d]						
Chi-square = 8.61 p<.01						
Total High LEDS Ratings	1.66	1.11	2.47	2.49	6.16	0.01

[a] Effect size = estimated regression coefficient / estimated standard error

[b] Includes cortisol diurnal average: mean of all five samples throughout the day (nmol/L)

[c] Includes cortisol post-peak average: mean of 2 PM, 4 PM, and bedtime samples in nmol/L

[d] Includes CAR = Cortisol Awakening Response percent change from awakening to 30 minutes later

MCI = Mild Cognitive Impairment
APOE-e4 = Apolipoprotein-E e4 allele
LEDS = Life Events and Difficulties Schedule
OR = odds ratio
CI = confidence interval

Table 4

Variables retained in logistic regression analyses with conversion from **CN to MCI** over individualized follow-up as the dependent variable and age at baseline (years), education (years), gender, presence or absence of APOE-e4 allele, total high LEDS ratings over follow-up, and a designated cortisol measure over follow-up as predictor variables.

Variables	OR	95% CI for OR		Effect Size [a]	Wald	p-value
Model 1 [b]						
Chi-square = 10.23 p<.01						
Age	1.26	1.03	1.53	2.26	5.08	0.02
Education	0.74	0.54	1.00	1.95	3.81	0.05
Model 2 [c]						
Chi-square = 10.23 p<.01						
Age	1.26	1.03	1.53	2.26	5.08	0.02
Education	0.74	0.54	1.00	1.95	3.81	0.05
Model 3 [d]						
Chi-square = 18.69 p<.001						
Age	1.40	1.08	1.83	2.51	6.34	0.01
Education	0.54	0.32	0.92	2.25	5.08	0.02
CAR percent change	0.96	0.93	1.00	2.00	4.23	0.04

[a] Effect size = estimated regression coefficient / estimated standard error

[b] Includes cortisol diurnal average: mean of all five samples throughout the day (nmol/L)

[c] Includes cortisol post-peak average: mean of 2 PM, 4 PM, and bedtime samples (nmol/L)

[d] Includes CAR = Cortisol Awakening Response percent change from awakening to 30 minutes later

CN = cognitively normal
MCI = Mild Cognitive Impairment
APOE-e4 = Apolipoprotein-E e4 allele
LEDS = Life Events and Difficulties Schedule
OR = odds ratio
CI = confidence interval